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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/627,592

07/25/2003

Peter B. Vander Horn

020130-001420US

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20350 7590 03/09/2007  
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EXAMINER

LUNDGREN, JEFFREY S

ART UNIT

PAPER NUMBER

1639

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
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3 MONTHS

03/09/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

## Office Action Summary

Application No.

10/627,592

Applicant(s)

VANDER HORN, PETER B.

Examiner

Jeff Lundgren

Art Unit

1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 01 December 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-5 and 17-19 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-5 and 17-19 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

Art Unit: 1639

## **DETAILED ACTION**

### ***Request for Continued Examination Under 37 CFR § 1.114***

A Request for Continued Examination under 37 CFR § 1.114, including the fee set forth in 37 CFR § 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR § 1.114, and the fee set forth in 37 CFR § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 1, 2006, has been entered.

### ***Status of the Claims***

Claims 1-5 and 17-19 are pending in the instant application, and are the subject of the Office Action below.

### ***Claim Rejections - 35 USC § 112, second paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

### **Previous Rejections Overcome by Amendment**

The previous rejections of claims 1-5 and 17-19 in the Final Office Action mailed on June 1, 2006, have been overcome by Applicant's amendments to the claims.

### **New Grounds of Rejection**

Claims 1-5 and 17-19 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claim 1, and all claims dependent therefrom, are indefinite for reciting the phrase "minimal nucleic acid coding sequence" because one of ordinary skill in the art could not reasonably determine the metes and bounds of this limitation. The phrase is not a term of art, nor is it defined in the specification. If instead, Applicant intends to claim a "minimal encoding nucleotide sequence," as set forth in the specification, such correction should be made.

Art Unit: 1639

Claim 1, and all claims dependent therefrom, for reciting the phrase “*the* minimal encoding sequences for the mismatched positions” because there is no antecedent basis. Correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 17-19, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

**Previous Rejection Withdrawn**

The previous rejection of claims 1-5 and 17-19, for having new matter is withdrawn in view of Applicant's amendment to the claims.

**New Grounds of Rejection**

Claims 1-5 and 17-19 are rejected for having new matter, specifically, the phrase “minimal nucleic acid coding sequence” is not reasonably supported by the specification. Applicant may overcome this rejection by replacing this phrase with “minimal encoding sequences.”

***Maintained Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The rejection of claims 1-3 and 5 are rejected under 35 U.S.C. 102(a) as being anticipated by Ness *et al.*, *Nature Biotechnology* 20:1251-1255 (2002), is maintained.

Claim 1 has been amended, and recites a method of creating hybrid proteins, wherein a step of selecting at least two parental proteins that have greater than 60 % amino acid similarity and a common activity, determining a minimal encoding sequence, creating a library of 32 or more nucleic acids, expressing the protein, and selecting a protein having a common property to the parent.

Ness teaches a synthetic shuffling method and evolutionary protein engineering technology in which every amino acid from a set of parent proteins is allowed to recombine independently of every other amino acid. Ness teaches that with the use of degenerate oligonucleotides, synthetic shuffling provides a direct route from database sequence information to functional libraries. Ness also teaches that physical starting genes are unnecessary (see *Abstract* and the introductory paragraphs). Ness teaches starting with a family of parent subtilisin genes; at least two parent sequences having greater than 60% amino acid similarity (see *Results and Discussion*, and Table 1). Next, Ness teaches the sequence conversion step:

“...[we] converted their DNA sequences to maximize sequence identity and conformity to the *Bacillus subtilis* codon usage table, and designed a series of oligonucleotides that encoded all variations in these genes. Differences in sequences between parental genes were incorporated either as degeneracies in the oligonucleotide or by using alternative non-degenerate oligonucleotides (see Fig. 1 for design strategy, Supplementary Table 1 online for oligonucleotide sequences, and Experimental protocol for the design and assembly protocol).”

Ness, page 1252, col. 1, first paragraph. Ness teaches the expression and testing of the hybrid proteins and selecting proteins having a common biological activity to the parent proteins (see page 1252, cols. 1 and 2).

Claim 2 requires that the parent proteins are enzymes and claim 3 requires isozymes; Ness teaches serine protease subtilins and teaches that these enzymes are from a family of serine protease subtilins/isozymes (see page 1251, col. 2). Claim 5 is directed to at least two parents having greater than 80% similarity and the majority of the library members have greater than

Art Unit: 1639

80% similarity; Ness teaches this similarity (see Figure 4 sequence comparison and description thereof).

Applicant contends that the Declaration under 37 C.F.R. § 1.131 signed by Inventor Vander Horn stating conception of the claimed invention and reduction to practice antedates the reference of Ness. Applicant states that the evidence provided as Appendix A and Appendix B are supportive of conception and reduction to practice of the claimed invention. Appendix A lists a series of nucleotide sequences by project code name, their length, scale, purity and cost. Appendix B is stated to show a gel showing hybrid proteins produced from the polynucleotides of Exhibit A that have polymerase activity.

However, Applicant's Declaration does not properly establish conception of the invention, or its reduction to practice, for at least the following reasons.

First, claim 1 requires a selection step in step a):

“selecting at least five mismatched positions in a protein sequence alignment of at least two parent proteins that have 60% or greater amino acid similarity and at least one common biological activity, wherein at a mismatched position, the parent protein sequences have different amino acids;”

Although Applicant alleges that the parent proteins are a Pfu polymerase and Deep Vent® polymerase in there Declaration, these identifiers are not conveyed in Appendix A. Futher, nowhere in Appendix A or B is it evidenced that the above-captioned step was conceived in the construction of the oligonucleotide sequences from the two parent protein sequences. There is no record that the parents shared a certain percent homology, nor is there a record that at least oligonucleotide library was generated by “selecting at least five mismatched positions.”

Claim 1 also recites step of determining a “minimal [encoding] sequence” in step b):

“determining a minimal nucleic acid coding sequence encoding the hybrid proteins, where for each mismatched position:  
the minimal nucleic acid coding sequence comprises a degenerate codon encoding an amino acid residue at the mismatched position, where the degenerate codon comprises at least one degenerate nucleotide position and the presence of the degenerate nucleotide position results in a codon that alternatively encodes the different amino acids in the parent proteins sequence at that mismatched position when the minimal encoding nucleic acid sequence is synthesized;”

Art Unit: 1639

Appendix A provides no description or indication as to the method that Applicant used in selecting the oligonucleotide sequence, and is not clear if all of the sequences presented (or at least 32 sequences) fall within this scope. Note: certain embodiments described in Applicants' specification are out the scope of claim 1, for example, the description in paragraph 0077. The claim only allows for selection of one of the two amino acids from the parent (i.e., the degenerate nucleotide position results in a codon that alternatively encodes the different amino acids *in the parent proteins*). The same argument holds for step c).

Furthermore, none of the evidence in Appendix B provides the proper support lacking in Appendix A in establishing conception or reduction to practice for the reasons above.

Accordingly, the rejection is maintained.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The rejection of claims 1-5, 17 and 19, are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ness *et al.*, *Nature Biotechnology* 20:1251-1255 (2002), in view of Xia *et al.*, *PNAS* 99(10):6597-6602 (2002), is maintained.

Applicant alleges that the rejection is overcome based on the filing of the Declaration.

However, this rejection is maintained for the reasons provided above indicating that the Declaration neither establishes conception or reduction to practice.

Claim 1 has been amended, and recites a method of creating hybrid proteins, wherein a step of selecting at least two parental proteins that have greater than 60 % amino acid similarity and a common activity, determining a minimal encoding sequence, creating a library of 32 or more nucleic acids, expressing the protein, and selecting a protein having a common property to the parent.

Ness teaches a synthetic shuffling, and evolutionary protein engineering technology in which every amino acid from a set of parent proteins is allowed to recombine independently of every other amino acid. Ness teaches that with the use of degenerate oligonucleotides, synthetic shuffling provides a direct route from database sequence information to functional libraries. Ness also teaches that physical starting genes are unnecessary (see *Abstract* and the introductory paragraphs). Ness teaches starting with a family of parent subtilisin genes; at least two parent sequences having greater than 60% amino acid similarity (see *Results and Discussion*, and Table 1). Next, Ness teaches the sequence conversion step:

“...[we] converted their DNA sequences to maximize sequence identity and conformity to the *Bacillus subtilis* codon usage table, and designed a series of oligonucleotides that encoded all variations in these genes. Differences in sequences between parental genes were incorporated either as degeneracies in the oligonucleotide or by using alternative non-degenerate oligonucleotides (see Fig. 1 for design strategy, Supplementary Table 1 online for oligonucleotide sequences, and Experimental protocol for the design and assembly protocol).”

Ness, page 1252, col. 1, first paragraph. Ness teaches the expression and testing of the hybrid proteins a selecting proteins having a common biological activity to the parent proteins (see page 1252, cols. 1 and 2).

Claim 2 requires that the parent proteins are enzymes and claim 3 requires isozymes; Ness teaches serine protease subtilins and teaches that these enzymes are from a family of serine protease subtilins/isozymes (see page 1251, col. 2). Claim 5 is directed to at least two parents having greater than 80% similarity and the majority of the library members have greater than 80% similarity; Ness teaches this similarity (see Figure 4 sequence comparison and description thereof).

Although Ness teaches a method directed to identifying mutant enzymes with improved thermostability (page 1251, col. 1), Ness does not explicitly teach improved thermostable polymerases as required by claims 4 and 17. And although Ness teaches starting with mismatched amino acid sequences, Ness does not explicitly teach the value twenty as in claim 19.

Xia teaches a method for identifying polymerases that have been selectively mutated for enhanced activity. Xia teaches that *in vitro* evolution is a powerful tool for generating the library of polymerase, wherein any number of approaches can be used prior to Xia's screening process, including, "cassette mutagenesis (1, 2), error prone PCR (3, 4), staggered extension process PCR (5), and gene shuffling (6, 7)." Xia, at page 6597, col. 1. The benefits of producing novel and improved polymerase are stated:

"The manipulation of DNA polymerase activity has attracted a great deal of attention because of the central roles of polymerases in biological processes as well as their utility in biotechnology applications. Earlier efforts to modify polymerase activity have focused largely on the rational design of site-directed mutants. For example, significant effort has been directed toward mutagenizing a DNA polymerase into an RNA polymerase (RNAP) (12, 13). Mutants that extend DNA primers by the incorporation of single ribonucleoside triphosphates (rNTPs) have been constructed; however, mutants that efficiently add successive rNTPs have proven more difficult to isolate. Moreover, in all reported cases, the mutant enzyme still prefers the dNTP substrates. The limited success of the rational approach likely results from the limited sequence space of the polymerases examined in these experiments. In vitro evolution strategies in which large populations of mutants are sampled for those with the desired activities are more likely to be successful, especially for rare activities."

Xia, at page 6597, col. 1.

One of ordinary skill in the art would have been motivated by the teachings of Ness, to prepare a library of chimeras from at least two homologous polymerases as taught by Xia, because of the advantages of Ness' method for improved directed evolution *via* synthetic shuffling. One of ordinary skill in the art would have appreciated the advantages of using parent proteins having high homology and the degeneracy approach, as taught by Ness, because of the increased diversity that is introduced when compared to more conventional shuffling means (see

Art Unit: 1639

Figure 2, and description thereof), and its application to all useful enzymes including serine proteases and thermostable polymerases. Regarding the limitation of twenty amino acid mismatches as in claim 19, and the various percentages of sequence similarity, these limitations would be considered obvious to one of ordinary skill in the art because these limitation merely represent a duplication of parts<sup>1</sup>, and routine optimization<sup>2</sup>, respectively, in view of the teachings of Ness. Accordingly, the invention as a whole was *prima facie* obvious at the time it was invented.

The rejection of claims 1-5 and 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ness *et al.*, *Nature Biotechnology* 20:1251-1255 (2002), in view of Xia *et al.*, *PNAS* 99(10):6597-6602 (2002) as applied to claims 1-5, 17 and 19 above, and further in view of Slater *et al.*, U.S. Patent No. 6,077,664, issued June 20, 2000, is maintained.

Applicant alleges that the rejection is overcome based on the filing of the Declaration.

However, this rejection is maintained for the reasons provided above indicating that the Declaration neither establishes conception or reduction to practice.

The limitations of claims 1-5, 17 and 19, along with the corresponding limitations taught in the art, have been detailed above, and are hereby incorporated by reference.

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<sup>1</sup> *In re Harza*, 274 F.2d 669, 124 USPQ 378 (CCPA 1960). (Claims at issue were directed to a water-tight masonry structure wherein a water seal of flexible material fills the joints which form between adjacent pours of concrete. The claimed water seal has a "web" which lies in the joint, and a plurality of "ribs" projecting outwardly from each side of the web into one of the adjacent concrete slabs. The prior art disclosed a flexible water stop for preventing passage of water between masses of concrete in the shape of a plus sign (+). Although the reference did not disclose a plurality of ribs, the court held that mere duplication of parts has no patentable significance unless a new and unexpected result is produced.

<sup>2</sup> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be *prima facie* obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969), - claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions).

Art Unit: 1639

Neither Ness or Xia explicitly teaches that the source of the polymerase is from *Pyrococcus furiosus*.

Slater teaches compositions of thermostable DNA polymerases derived from the hyperthermophilic eubacteria, and teaches methods for utilizing naturally-occurring and non-naturally-occurring forms of *T. neopolitana* DNA polymerase (see *Summary of the Invention*). The *T. neopolitana* DNA polymerases taught by Slater are used in combination with other compounds, including but not limited to pyrophosphatase and DNA polymerases from other thermophilic or hyperthermophilic organisms, such as *Pyrococcus furiosus*, which are known in the art to be high fidelity polymerases (col. 12, lines 43-52).

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Slater, Xia and Ness teach methods for producing hybrid enzymes with increase biological activity from native sources through various shuffling methods. One of ordinary skill in the art would have been motivated to utilize one polymerase from *Pyrococcus furiosus* as one of the other parent polymerases, as in Slater, in order to incorporate sequence elements imparting high fidelity into certain of the hybrid proteins produced by the method of Ness. Accordingly, the invention as a whole was prima facie obvious at the time it was invented.

Accordingly, the rejection is maintained.

### ***Conclusions***

No claim is allowable.

If Applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsius verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Art Unit: 1639

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James Schultz, can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JSL

  
MARK L. SHIBUYA  
PRIMARY EXAMINER